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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/261,537	06/17/94	STEINMAN R	20164000US3

18M2/0904

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EXAMINER	
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ART UNIT	PAPER NUMBER
1808	12

DATE MAILED:
09/04/96

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary	Application No. 08/261,537	Applicant(s) Steinman et al
	Examiner L. Blaine Lankford	Group Art Unit 1808

☒ Responsive to communication(s) filed on *6-25-96 and 8-19-96*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-23* is/are pending in the application.

Of the above, claim(s) *14-21* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-13, 22, and 23* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

JOHN W. ROLLINS
PRIMARY EXAMINER
ART UNIT 183

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Part III DETAILED ACTION

Claims 1-23 are currently pending in the instant application. Claims 14-21 are withdrawn from consideration as being drawn to non-elected subject matter. Accordingly, claims 1-13 and 22-23 have been examined on the merits.

The rejections under 35 USC 112 second paragraph have been overcome by applicant's amendment.

The declaration under 37 CFR 1.131 has been considered but is adequate to overcome the Sallusto et al reference, because neither the fax nor the declaration detail when the fax was sent.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability

under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-5 and 10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Markowicz et al.

Markowicz et al. teach a method of producing a population of dendritic cells. The method comprises providing a population of cells from human peripheral blood which comprises dendritic cells. The dendritic cells were then cultured in microwells containing supplemented RPMI-1640 medium, 10% heat-inactivated human serum and 100 U/ml of GM-SCF. Markowicz et al. further teach that the culture medium could additionally be supplemented with IL-4.

Accordingly, the claims would have been anticipated by one of ordinary skill in the art at the time the claimed invention was made.

Claim 22 is rejected under 35 U.S.C. § 102(b) as anticipated by or, in the

alternative, under 35 U.S.C. § 103 as obvious over Markowicz et al.

Markowicz et al., relied upon for the reasons discussed *supra*, teach the production of dendritic cells.

The Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether or not applicants' cells differ and, if so, to what extent, from the cells discussed in the references. Accordingly, in as much as the examiner has established that the prior art cells, which are obtained from the same source and produced by the same method as that claimed, she has reasonably demonstrated a reasonable likelihood/possibility that the compared cells are either identical or sufficiently similar that whatever differences exist are not patentably significant. Therefore, the burden of establishing non-obviousness by objective evidence shifted to applicants.

Accordingly, the claimed invention would have been at least *prima facie* obvious, if not anticipated, to one of ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

Applicant's arguments have been fully considered but they are not deemed to be persuasive. The Markowicz reference appers to contain all the claimed elements as precursor cells are exposed to GM-CSF- applicant's distinction is not clear.

Claims 6 and 11-12 are rejected under 35 U.S.C. § 103 as being unpatentable over Markowicz et al. as applied to claims 1-5 and 10 above, and further in view of

Jakoby et al.

Markowicz et al., relied upon for the reasons discussed *supra*, teach utilization of 100 U/ml of GM-CSF and IL-4. Markowicz et al. differs from the claimed invention by not specifically indicating the exact concentration level of IL-4 utilized and also by teaching the utilization of a slightly less concentration level of GM-CSF from that which is specifically claimed. However, it is well known in the art to adjust the concentration level of culture medium additives in order to optimize the experimental conditions for the particular cell type being cultured. Jakoby et al., on pages 75-77, teach that it is well known in the art of cell culture to "tailor media" in order to optimize the experimental conditions. Each culture system requires examination of the particular conditions that are best for the type of cell being studied by the investigator. Furthermore, each component of the system, identified as result-effective variables, has its well recognized advantages for the purpose of optimizing the experimental conditions. This type of optimizing experimental conditions is well within the purview of the skilled artisan and is deemed a matter of routine experimentation.

Accordingly, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

Applicant's arguments have been fully considered but they are not deemed to be persuasive. In response to Applicant's piecemeal analysis of the references, it has been held that one cannot show non-obviousness by attacking references individually where,

as here, the rejections are based on combinations of references. *In re Keller*, 208 USPQ 871 (CCPA 1981). Jakoby is provided as a showing that optimization of cell culture components was old and well known in the art and thus obvious to one of ordinary skill in the art.

Claims 7 and 13 are rejected under 35 U.S.C. § 103 as being unpatentable over Markowicz et al. as applied to claims 1-5 and 10 above, and further in view of Koch et al.

Markowicz et al. differs from claim 8 by not specifically teaching that the culture medium may further comprise TNF-alpha.

Koch et al teach that new insight into the biology of dendritic cells (DC) came from studies of murine epidermal Langerhans cells (LC) *in vitro*. Koch et al. indicate that such studies have suggested that LC in the skin and DC in other non-lymphoid tissues represent precursors or immature elements of the dendritic cell system. Koch et al. teaches that the addition of TNF-alpha to murine epidermal Langerhans cells in culture allows such cells to maintain their viability. Therefore, in view of the teachings of Koch et al., one of ordinary skill in the art would have a reasonable expectation of success in maintaining viability of dendritic cells when TNF-alpha is added to a dendritic cell culture. Accordingly, one of ordinary skill in the art would have had a reasonable expectation of success in adding TNF-alpha to the dendritic cell culture of Markowicz et al. As decided in In re O'Farrel, 7 USPQ 2d 1673 (Fed. Cir. 1988), obviousness does not require

absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious. In re Merck & Co., 800 F.2d at 1098, 231 USPQ at 380; Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1461, 221 USPQ 481, 488 (Fed. Cir. 1984); In re Papesch, 315 F.2d 381, 386-387, 137 USPQ 43, 47-48 (CCPA 1963). For obviousness under 35 U.S.C. 103, all that is required is a reasonable expectation of success. In re Longi, 759 F.2d 887, 897, 225 USPQ 645, 651-652 (Fed. Cir. 1985); In re Clinton, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976).

In conclusion, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

Applicant's arguments have been fully considered but they are not deemed to be persuasive. In response to Applicant's piecemeal analysis of the references, it has been held that one cannot show non-obviousness by attacking references individually where, as here, the rejections are based on combinations of references. *In re Keller*, 208 USPQ 871 (CCPA 1981). Koch is provided to demonstrate the obvious use of TNF-α in cell culture of this variety.

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Claims 8-9 and 23 are rejected under 35 U.S.C. § 103 as being unpatentable over Markowicz et al. as applied to claims 1-5 and 10 above, and further in view of Voorhis et al or Ruley et al.

Markowicz et al. differs from claims 8-9 and 23 by adding 10% heat-inactivated human serum as opposed to 1-15% fetal calf serum or 5% cord blood serum. However, Voorhis et al teach that human dendritic cells may be cultured in 5-10% fetal calf serum. Furthermore, it is well known in the animal cell culture field to utilize cord blood serum in animal cell cultures. *See, e.g.,* Ruley et al., U.S.Patent No. 5,364,783, column 22, lines 21-27. Therefore it is deemed merely a matter of judicious selection on the part of the skilled artisan to utilize fetal calf serum or cord blood serum as opposed to human serum. Additionally, it is well known in the art to utilize anywhere from 1-20% of serum in animal cell cultures. Utilization of a particular concentration within that range is deemed merely a matter of routine optimization which is well within the purview of the skilled artisan.

Accordingly, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

Applicant's arguments have been fully considered but they are not deemed to be persuasive. In response to Applicant's piecemeal analysis of the references, it has been held that one cannot show non-obviousness by attacking references individually where, as here, the rejections are based on combinations of references. *In re Keller*, 208 USPQ 871 (CCPA 1981). Voorhis et al and Ruley et al have been cited to demonstrate that the

art teaches that serum is useful in nerve cell cultures.

The arguments regarding the rejections based on the Hueffler reference are convincing and those rejections are hereby withdrawn.

No claim is allowed.

I. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

II. Any inquiry concerning this communication or earlier communications from the examiner should be directed to L. Blaine Lankford whose telephone number is (703) 308-2455.

JOHN W. ROLLINS
PRIMARY EXAMINER
ART UNIT 183

LBL
September 3, 1996